REMARKS

Claims

Claims 1–8 are currently under examination. Claim 9 is added by this paper.

Claim amendments

The claims have been amended according to conventional US practice. The amendments do not change the scope of the claimed subject matter.

Claim 9 recites the subject matter cancelled from claim 2.

Applicants respectfully submit that the amendments presented herein do not raise new matter. Entry thereof is earnestly solicited.

Claim objections

The Examiner is thanked for her careful reading of the claims. The objection of claim 2 is moot in view of the amendment of the claim.

Sequence Listing

Applicants have contacted a sequence vendor to attend to the objection of the specification for allegedly failing to provide sequence identifier numbers of the biological sequences recited therein. The Examiner is requested to hold this objection in abeyance until such can be furnished. See, MPEP §714.02.

Rejection under 35 U.S.C. §102(e)

Claims 1–4 and 6 are rejected under §102(e) as allegedly anticipated by Chiarello (US patent No. 7,183,405; hereinafter "the '405 patent). The '405 patent stems from US serial No. 09/894,423 filed June 28, 2001, which is a continuation-in-part of US serial No. 09/344,226, filed June 25, 1999. This rejection is respectfully traversed.

Chiarello describes a method of labeling oligonucleotides by (a) providing a solid support-bound oligonucleotide having an amino group, a bifunctional linker arm and an activated label; (b) reacting the solid support-bound oligonucleotide with the bifunctional linker arm to produce a support-bound linker-oligonucleotide; and (c) reacting the support-bound linker-oligonucleotide with the activated label to produce a labeled support-bound oligonucleotide. Chiarello further contemplates that optionally, the amino group of the support-bound protected linker-oligonucleotide can be deprotected to produce a support-bound deprotected linker-oligonucleotide, which is then reacted with the activated label. See col. 2, lines 3–35 of the '405 patent. As outlined

in detail in Figs. 1 and 2, the solid support-bound oligo comprises a free-hydroxyl group on the 5' sugar residue, which is to be coupled to a label (i.e., tetramethyl rhodamine or TMR) comprising a bifunctional linker (i.e., phosphoramidite). The '405 patent is silent with respect to the structural aspects of the claimed oligonucleotide molecule. More specifically, there is no mention of a labile orthogonal protecting group that is bound to a terminal hydroxy group, as claimed herein. See also the subject matter of claims 6 and 7. In Chiarello, the terminal hydroxyl group is *free*, for example, to react with the phosphoramidated TMR. See, Figs. 1A and 1B. Additionally, Chiarello does not teach or suggest the claimed reaction scheme, for example, wherein the labile orthogonal protecting group is at least partially substituted by the labeling compound in a nucleophilic substitution reaction. In contrast, the labeling moiety in Chiarello is coupled to the oligo in an *addition-oxidation* reaction.

Since not all aspects of the present claims are taught or disclosed by Chiarello, the entirety of the disclosure in the '405 patent fails to anticipate the subject matter of the instant invention. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §103(a)

Claims 5 and 7-8 are rejected under §103(a) as allegedly rendered obvious by the aforementioned Chiarello in view of Beier (DE 19915867, which corresponds to US Patent No. 6,756,492) further in view of Urdea (US Patent No. 5,703,218). This rejection is respectfully traversed.

The Office Action asserts that Beier teaches oligonucleotide synthesis comprising photolabile groups, such as, carbonate ester and alleges that the aforementioned Chiarello et al. in view of Beier renders obvious the subject matter of claims 5 and 7-8.

The Examiner's rationale for *prima facie* obviousness is provided in the paragraph bridging pages 5 and 6 of the Office Action, wherein it is stated:

> Therefore it would have been obvious at the time the invention was made to manufacture an oligonucleotide conjugate as taught by Chiarello, where in the oligonucleotide conjugate is bound to the a solid support a the 5'-end and having a carbonate protective group. It is well in the art to attach the oligonucleotide on the 5' or 3'-end. Also carbonate protective are particularly useful in the chemical synthesis of linear or branched oligonucleotide structure as they are readily removed with mild reagents. (Urdea abstract). Further it is well known in the art of organic chemistry to

control the removal of the protective group and therefore be partially removed by controlling the reaction conditions, reagents concentration, etc.

Applicants respectfully disagree with this reasoning and the rejection based thereon.

The limitations of Chiarello have been outlined *supra*. For example, Chiarello's disclosure of solid-support bound oligos and methods of coupling them to phosphoramidated tetramethyl rhodamine (TMR) fails to anticipate the claimed methods. Moreover, Chairello requires the use of bi-functional linkers, such as, phosphoramidites, to derivatize the label prior to coupling to the oligonucleotide. The methods of the instant invention are not limited by such aspects. Accordingly, the claimed invention is both novel and unobvious over Chairello.

The secondary reference of Beier teaches nucleoside analogs with photo-unstable protecting groups. Beier teaches generic methods for generating nucleic acid chips using 3'-photolabile nucleosides, in which the oligomers built up by light-controlled synthesis are linked to the solid phase via the 5' end and thus enable enzyme reactions at the 3' end. See, SUMMARY OF INVENTION section of the '492 patent. The photo-unstable protecting groups are used for an entirely different purpose in Beier. For example, Beier fails to teach or suggest the use of labile protecting groups which can be at least partially substituted by the labeling compound in a nucleophilic substitution reaction. Accordingly, Beier does not rectify the limitations of Chairello. It is submitted that the totality of the disclosure in references does not lead one of ordinary skill in the art to arrive at the presently claimed methods, for example, methods for manufacturing an oligonucleotide conjugate comprising employing a nucleophilic substitution reaction. Obviousness requires a suggestion of all the elements in a claim (*CFMT Inc., v Yieldup Int'l Corp.* 349 F.3d 1333, 1342 [68 USPQ2d 1940] (Fed. Cir. 2003)) and requires a reason that would have prompted [a skilled worker] to combine the elements in the way the claimed new invention does. *Ex parte Alexander* (Decided November 30, 2007; *86 USPQ2d 1120).* Since such has not been established by the Office Action, at least with respect to the features of the labile protecting group, the PTO's contentions regarding *prima facie* obviousness are without merit.

In view of the above remarks, favorable reconsideration is courteously requested. If there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response to Deposit Account No. 13-3402.

Respectfully submitted,

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